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Reprinted from The Journal of the American Medical Association
April 1, 1916, Vol. LXVI, pp. 998-1000

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A great many theories have been advanced concerning the cause of gastric ulcer. The main feature of most of these theories is that there is a decreased resistance of limited areas of the gastric wall followed by the digestion of these areas by the unrestricted action of the pepsin. The investigation reported in this paper is concerned with the cause of this diminished resistance. It has been recognized for a long time that the resistance to the action of the digestive juices of limited portions of the mucosa of the stomach is decreased by cutting off the blood supply to these portions as, for example, by a clot in a small blood vessel (thrombosis) or by the ligation of the vessel. Under such conditions the area is digested by the pepsin with the formation of an ulcer. The decreased resistance of the areas rendered anemic by cutting off the blood supply has usually been attributed to the deprivation of the areas of nutrition. The frequency of the occurrence of gastric ulcer among anemic persons has led many to consider anemia a predisposing factor in the production of ulcer. Lesions produced in the mucosa of normal healthy animals heal, as a rule, with more or less ease. If, however, the animal is rendered anemic by bleeding or by the introduction of some hemolytic agent, lesions in the gastric mucosa heal very tardily. When the blood supply to a portion of the mucosa is cut off, among other things, the part is deprived of oxygen, and for that reason the oxidative processes are decreased.

Araki[1] showed that the oxidative processes are decreased in rabbits rendered anemic by bleeding. In

* From the Physiological Laboratory of the University of Illinois.
1. Araki: Ztschr. f. physiol. Chem., 1894, xix, 424.

phosphorus poisoning the oxidative processes of the body are decreased,[2] and it has been observed that under these conditions the tendency of the tissues to undergo autolysis is increased.[3] In diseases of the circulatory and respiratory systems, where the amount of oxygen is decreased and hence the oxidative processes are decreased, there is a great tendency of all the tissues to undergo self-digestion.[4] These facts would seem to point to some relation between the oxidative processes of the body and the resistance of the tissues to the digestive action of the proteolytic enzymes. Burge[5] showed that pepsin as well as trypsin is easily destroyed by oxidation. Lillie[6] showed that the cells of the gastric mucosa possess intense oxidative properties.

In view of the fact that pepsin is easily destroyed by oxidation, that the cells of the mucosa possess oxidative properties, and that these cells become easily digested when these properties are decreased, the hypothesis is advanced that the mucosa is not digested under normal conditions because the pepsin immediately in contact with the wall of the stomach is rendered inert by the oxidative processes of the cells. This theory assumes that normally a balance exists between the oxidative processes of the cells of the mucosa and the digestive action of the pepsin in the stomach. If this balance is destroyed, as for example by depriving a limited area of oxygen by cutting off the blood supply, thereby decreasing the oxidative processes of the area, this area should be digested by the pepsin with the production of ulcer. That the mucosa is digested with resulting ulcer under such a condition has been verified by many observers.

REPORT OF EXPERIMENTS

The following experiments were devised to imitate the protective mechanism as set forth in the foregoing hypothesis:

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2. Welsch: Arch. internat. de pharmacod. et de therap., 1905, xiv, 211. Ries: Berl. klin. Wchnschr., 1905, xlii, 44a, 54.
3. Jacoby: Ztschr. f. physiol. Chem., 1900, xxx, 174.
4. Schlesinger: Beitr. z. chem. Physiol. u. Path. (Hofmeister's), 1904, iv, 87.
5. Burge: Am. Jour. Physiol., 1915, xxxvii, 462.
6. Lillie: Am. Jour. Physiol., 1902, vii, 413.

In Figure 1, *a* is a rubber cuff holding vessels *b* and *c* in position as indicated; *d*, a piece of platinum mesh tied over the end of cylinder *b*, and *e* a piece of gastric mucosa of the dog tied over the platinum mesh. Before the platinum mesh was tied over the end of the cylinder, platinum black was deposited on it by means of the direct electric current. To 15 c.c. of gastric juice of the dog, 15 c.c. of hydrogen peroxid were added, and the resulting solution was made acid with hydrochloric acid to the same extent as the original gastric juice. This solution was poured into cylinder *b*, and the whole preparation placed in a water bath at 38 C. (100.4 F.). Immediately after the solution was poured into the cylinder,

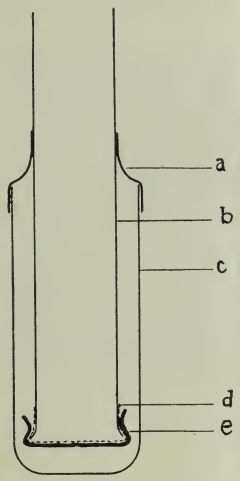


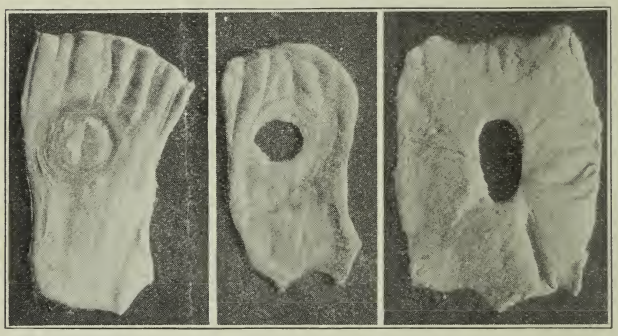
Fig. 1.—Diagram of apparatus: *a*, rubber cuff holding glass vessels *b* and *c* in position; *d*, platinum mesh; *e*, piece of gastric mucosa.

an evolution of oxygen gas was observed in the region of the platinum mesh. This, of course, was due to the decomposition of the hydrogen peroxid by the platinum black. Thus the mucosa was exposed to the action of the gastric juice in the presence of atomic oxygen. After six hours, the piece of mucosa was removed from the tube and photographed (Fig. 2 *A*). It may be seen that the central circular area exposed to the action of the gastric juice in the presence of atomic oxygen had not been digested.

Another preparation, similar to the one described, except that no platinum black was deposited on the platinum mesh, was made and placed in the water bath at 38 C. On addition of the gastric juice diluted with hydrogen peroxid no oxygen was given off, there being no platinum black on the mesh; hence this piece of mucosa was exposed to the action of the

gastric juice in the absence of atomic oxygen. Figure 2 *B* is a photograph of the piece of mucosa after the preparation had been in the bath for sixty-five minutes. It may be seen that the central circular area exposed to the action of the gastric juice had been completely digested with the formation of a hole. In Figure 2 *A* the oxidation produced by the atomic oxygen liberated at the surface of the dead mucosa protected it, while in Figure 2 *B*, no such protection being afforded, the exposed circular area was readily digested with the production of what corresponds to gastric ulcer. Figure 2 *C* is a perforating ulcer of the stomach shown for comparison.

The following experiments were carried out on unicellular organisms to show that when they are introduced into a solution of trypsin they protect themselves from being digested by means of their oxidative processes:



A B C

Fig. 2.—Pieces of gastric mucosa. The central areas of *A* and *B* were exposed to the action of gastric juice, *A* in the presence of atomic oxygen, *B*, in the absence of atomic oxygen. *C*, perforating ulcer of the stomach.

One hundred c.c. of clear pancreatic juice were collected from a cannula in the pancreatic duct of a dog as the result of the repeated injections of secretin into the jugular vein. The trypsinogen in this juice was converted into active trypsin by the addition of 5 c.c. of enterokinase. The resulting trypsin solution was sterilized by exposing it for a few minutes to ultraviolet radiation. It was then placed in a collodion tube and dialyzed against 5 liters of distilled water for twenty-four hours at 10 C. (50 F.) to get rid of most of the dissolved salts.

Five c.c. of the activated dialyzed juice were introduced into each of two long test tubes. Five drops of water con-

taining a great number of living parameciums were introduced into one tube and another five drops of water containing dead parameciums, killed by exposure to ultraviolet radiation, into the other. Both tubes were placed in a water bath at 30 C. (86 F.). At the end of three hours, the parameciums, killed by exposure to ultraviolet radiation before being introduced into the pancreatic juice, were completely digested, while those introduced alive were as active as at the beginning of the experiment. At the end of seventy-two hours, when the experiment was discontinued, these parameciums were still alive and very active.

These two experiments show, as has been recognized for a long time, that living cells are very resistant to the action of proteolytic enzymes, while dead cells are digested with more or less ease.

The digestive strength of the trypsin and the resistance of the living parameciums having been determined by these control experiments, an attempt was made to lower the resistance of the organisms to tryptic activity by decreasing their oxidative processes. Five c.c. of the activated dialyzed pancreatic juice were exposed to the radiation from a quartz mercury-vapor burner for one hour to destroy the trypsin. Living parameciums were introduced into this inactive juice, and hydrogen gas was bubbled through it for ten hours at 30 C. The purpose of bubbling the hydrogen gas through the juice was to deprive the parameciums of most of the oxygen dissolved in the liquid and thus decrease the oxidative processes of the parameciums. At the end of the ten hours the organisms were alive and active. This experiment shows that the hydrogen gas bubbled through the liquid was not injurious to the parameciums and that there remained in the liquid sufficient oxygen for the life processes of the organisms.

Five drops of water containing parameciums were introduced into 5 c.c. of the activated dialyzed pancreatic juice. Hydrogen gas was bubbled through this liquid as it had been through the inactive juice containing the parameciums. The organisms were observed under the microscope at frequent intervals during the experiment. After about two hours the animals were observed to move less rapidly than at the beginning of the experiment. A little later these slowly moving organisms became more transparent and moved more slowly. As digestion proceeded, the transparency of the parameciums increased, and at the end of the third hour the partially digested organisms appeared as shadows. About half an hour later these parameciums had been completely digested and had gone into solution. These organisms were literally digested while alive and killed by the action of the trypsin itself in the process of digestion.

The preceding experiment was repeated, and when the animals were partially digested, the bubbling of hydrogen

gas through the liquid was discontinued and the bubbling of oxygen gas was substituted. When this was done, the organisms that had not been too much digested were revived, and lived on as normal animals.

These experiments show that the resistance of these unicellular organisms to the digestive action of trypsin is greatly reduced when their oxidative processes are decreased, and that their resistance returns when the oxidative processes are restored. The results obtained on these living unicellular organisms would appear to lend support to the hypothesis advanced in explaining the resistance of the living cells of the gastric mucosa to the digestive action of pepsin.

CONCLUSIONS

The decreased resistance of a circumscribed area of the stomach to the digestive action of gastric juice is due to a decrease in the oxidative processes of the cells of the area. Gastric ulcer is due to the subsequent digestion of the area by pepsin.

The resistance of unicellular organisms (parameciums) to the digestive action of the proteolytic enzymes can be increased or decreased by increasing or decreasing the intensity of the oxidative processes of the organisms, the greater the intensity of the oxidative processes the greater the resistance, and vice versa.